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Wium-Andersen, M K; Villumsen, Martin Dalgaard; Wium-Andersen, I K; Jørgensen, M B; Hjelmborg, J B; Christensen, K; Osler, M

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PROFESSOR MERETE OSLER (Orcid ID : 0000-0002-6921-220X)

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Familial risk and heritability of depression by age at first diagnosis in Danish twins

Running title: Depression by age in Danish twins

Marie Kim Wium-Andersen[1], Martin Dalgaard Villumsen[2], Ida Kim Wium-Andersen[3], Martin Balslev Jørgensen[3,4], Jacob B Hjelmborg[2], Kaare Christensen[2], Merete Osler[1,5]

[1] Center for Clinical Research and Prevention, Bispebjerg and Frederiksberg Hospital, Denmark

[2] Department of Epidemiology, Biostatistics, and Biodemography, Institute of Public Health, University of Southern Denmark and the Danish Twin Registry, University of Southern Denmark

[3] Psychiatric Center Copenhagen, Rigshospital, Denmark

[4] Institute of Clinical Medicine, University of Copenhagen, Denmark

[5] Department of Public Health, Section of Epidemiology, University of Copenhagen, Denmark

Correspondence to:

Merete Osler; Center for Clinical Research and Prevention

Nordre Fasanvej 57, DK-2000 Frederiksberg, Denmark

Phone: +45 40104312, Email: Merete.osler@regionh.dk

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Objective: Familial and genetic factors seem to contribute to the development of depression but whether this varies with age at diagnosis remains unclear. We examined the influence of familial factors on the risk of depression by age at first diagnosis.

Methods: We included 23,498 monozygotic and 39,540 same-sex dizygotic twins from the population-based Danish Twin Registry, followed from 1977 through 2011 in nationwide registers. We used time-to-event analyses accounting for censoring and competing risk of death to estimate cumulative incidence, casewise concordance, relative recurrence risk, and heritability of first depression by age using monozygotic and same-sex dizygotic twin pairs.

Results: During follow-up, a total of 1545 twins were diagnosed with depression. For twins at age 35 or younger at first depression, heritability was estimated to be 24.8% (95% confidence interval [CI], 4.6-43.1%), whereas at age 90 it was 14.7% (95% CI, 3.1-26.3%). The relative recurrence risk was higher at younger ages: at age 35 the risk was 27.7-fold (95% CI, 20.0-35.5) and 6.9-fold (95% CI, 3.9-9.8) higher than the population risk for monozygotic and same-sex dizygotic twins, respectively, while the corresponding numbers were 3.0 (95% CI, 2.3-3.6) and 1.8 (95% CI, 1.3-2.2) at age 90. Heritability seemed similar for male and female twins.

Conclusion: Familial risk of depression, caused either by genes or shared environment, seemed to slightly decrease with age at diagnosis and an elevated concordance risk for monozygotic over same-sex dizygotic pairs suggested a genetic contribution to the development of depression.

Keywords: depression, heritability, familial influence, twin cohort

Significance: The degree to which familial factors overall and genetic factors specifically influence depression risk seems to depend on age of diagnosis and sex. Familial and genetic influence on depression decline with age at first diagnosis. Heritability seemed to be similar for male and female twins.

Limitations: Although the cohorts were relatively large, the sex-specific estimates based on depression diagnosis were less precise and it was not possible to study very early onset or recurrent depressive events. Hospital discharge diagnoses may not include the milder episodes of depression treated in primary care, nor the exact age of depression onset.

Data Availability Statement: The data that support the findings of this study are available from Statistics Denmark. Restrictions apply to the availability of the data that were used under license for this study. Data are available from Statistics Denmark with the permission of the scientific board of the Danish Twin Registry.

INTRODUCTION

Depression is a common psychiatric disease, most likely caused by a combination of genetic and environmental factors(1). Twin studies represent a unique possibility to evaluate both early familial influences and the genetic heritability of diseases(2). The rationale is that while monozygotic (MZ) twins share 100% of their genes and dizygotic twins (DZ) share 50% of their genes(3), the shared environment early in life is assumed to be similar within MZ and DZ twin pairs.

One of the first twin studies on depression was published in 1977 using data from 110 twin pairs born 1870-1920 from the Danish Twin Registry(4) and it showed that concordance rates for depression (i.e. co-occurrence of disease in a twin pair) were higher among MZ compared to DZ twins, suggesting a genetic contribution to the development of depression. Since then, several twin and family studies have provided evidence that depression is familial and moderately heritable, with an estimated heritability (estimated as the proportion of variability in depression risk in a population due to genetic factors) ranging between 33-54%(1,5). The importance of early environmental factors shared in families and genetic factors may depend on sex and age of onset. Thus, some studies indicate that the heritability of depression differs by sex(6,7), with female depression showing higher heritability than male. Further, it has been suggested that age of onset of depression may have differing genetic aetiology(8), as some studies have reported higher heritability estimates

for early compared to late-onset depression(9), whereas others showed no differences in heritability across age(10,11).

However, mortality risk varies with sex and age, being highest in males and older ages(12), but previous twin studies on depression have not addressed censoring or accounted for competing risk of death. Consequently, the aim of the present study was to examine familial risk and heritability by age at first diagnosis of depression using estimates of cumulative incidence, casewise concordance, relative recurrence risk (RRR), and heritability in a cohort of male and female MZ and same-sex dizygotic (ssDZ) twins.

METHODS

The twin population

The Danish Twin Registry was initiated in 1954 and was updated on several occasions(13). It contains information on multiple births from 1870 to 2009. Information on twin births between 1870-1930 was ascertained from the local clergy registers in every parish in Denmark, whereas twins births from later cohorts have been ascertained mainly via the Danish Civil Registration System(14). The completeness of the Danish Twin Registry varies over birth cohorts with approximately 90% up to 1968 to nearly 100% after 1968(15). Determination of zygosity is questionnaire-based with an overall misclassification rate of 4%(16). For this study, all same-sex (ss) twin pairs from the Danish Twin Registry where both twins were alive and not diagnosed with depression before January 1977 have been included. Because risk factors and incidence of depression vary between males and females, opposite-sex twin pairs (N=45,354 individuals) were excluded. In total, the twin study sample includes 23,498 MZ and 39,540 ssDZ twins.

The civil registration number of the Danish Civil Registration System, unique to all individuals in Denmark, made it possible to link all twins to the Danish Psychiatric Central Research Register(17), the Danish National Patient Registry(17), and the Danish Prescription Registry(18). Information on vital status and emigration has been taken from the Danish Civil Registration System.

Depression

Depression diagnoses were identified in the Danish Psychiatric Central Research Register and the Danish National Patient Registry and were defined as having any of the diagnoses F32-F33 according to the International Classification of Diseases (ICD) 10th edition and 296.09, 296.29, 298.0 or 300.49 according to the 8th edition, as the 9th edition was never implemented in Denmark. The Danish Psychiatric Central Research Register contains information on all psychiatric admissions to psychiatric hospitals or wards in Denmark from 1969 onwards(17). From 1995, all outpatient treatments and information from emergency rooms were also included and the register became an integrated part of the Danish National Patient Registry.

Not all depressed individuals are seen at psychiatric clinics or hospitals and, consequently, we used any prescription of antidepressants as secondary outcome. The prescriptions were identified by the Anatomic Therapeutical Chemical (ATC) classification system codes N06A in the Danish Prescription Registry. This register holds information on all prescribed and redeemed drugs sold at Danish pharmacies since 1995(19).

Statistical methods

Cohort members were followed for outcomes in registers from 1977 until either end of follow-up on December 31st, 2011, date of death, or emigration. Cumulative incidence of depression was estimated using the nonparametric Aalen-Johansen estimator(20) in a competing risk setting. Casewise concordance (an individual twin's risk of depression, given depression in the co-twin) was estimated by age(21,22). If the risk of depression is higher among twins with co-twins already diagnosed with depression than for the general twin population independent of the status of the co-twin (that is, if the casewise concordance for twins is higher than the cumulative incidence in the twin population), it suggests a familial effect that can either be due to shared family environment or genetics. Furthermore, if the casewise concordance is higher in MZ than in DZ twins, this suggests a genetic effect. Familial aggregation can be assessed using the recurrence risk ratio (RRR). The RRR is the ratio between the incidence of twin pairs concordant for the disease divided by the squared cumulative incidence function (CIF) of the disease in the twin cohort at a given age and is, as such, a different way of portraying familial and genetic effects. A RRR above 1 suggests a familial effect.

We also addressed censoring and took competing risk of death into account when we estimated the heritability of depression by age of depression onset(24). Due to few early-onset cases, the measures based on within-pair comparisons were only provided from age 35. Differences

of casewise concordance curves for MZ and ssDZ pairs from cumulative incidences were tested using Pepe and Mori tests(21). The analyses were repeated with stratification by sex. We also evaluated the representativeness of our incidence measures in supplementary analysis, including a population-based 5% sample of the non-twin Danish population. Further, we compared our estimates with a comprehensive study of lifetime risk of mental disorders in Denmark(23), using the same follow-up period from 2000-2011 (Supplementary Figure 1). All analyses were performed using STATA version 15 or the R software environment version 3.5.1.

RESULTS

We included 23,498 MZ and 39,540 ssDZ twins from the Danish Twin Registry. A total of 49% were females. During follow-up, a total of 538 (2.3%) of the MZ and 1,007 (2.6%) of the ssDZ twins had a diagnosis of depression and of these cases, 352 (65%) and 616 (61%) were in female MZ and ssDZ twins, respectively (Table 1). Further, 4,358 (18.5%) MZ and 7,206 (18.2%) ssDZ twins had redeemed antidepressant medication. The mean age at first depression diagnosis or use of antidepressant medication is shown in Table 1, in addition to the number of MZ and ssDZ twin pairs concordant or discordant on depression diagnosis. The sex-stratified cumulative incidence of depression and the secondary outcome in Figure 1 showed that the lifetime risk of being diagnosed with depression was 4.1% (3.6%-4.5%) for males and 7.2% (6.7%-7.9%) for females.

Figure 2 shows the casewise concordance of depression and the corresponding heritability by age at first diagnosis for MZ and ssDZ twins. At age 90, the casewise concordance risk was 14.8% (9.7%-19.9%) for MZ twins and 7.8% (5.0%-10.6%) for ssDZ twins. The casewise concordance risk of depression was significantly different from the cumulative incidence of depression for both MZ ($p<0.001$) and DZ twins ($p=0.002$), and there was a significant difference by age ($p=0.001$) between the casewise concordances for MZ and ssDZ twins. The indicated familial risk of depression, caused either by genes or shared environment, seemed to slightly decrease with age at diagnosis and the elevated risk for MZ over ssDZ pairs suggested a genetic contribution to the development of depression. The heritability of depression in relation to age at diagnosis is shown in the heritability plots with estimates listed at specific ages (Figure 2, middle and bottom). In twins aged 35 at depression diagnosis, the heritability was estimated to 24.8% (95% CI, 4.6-43.1%), whereas the heritability at diagnosis at age 90 was 14.7% (95% CI, 3.1-26.3%).

For the secondary outcome, the analyses indicated materially the same pattern of associations as for depression diagnosis, albeit with more narrow confidence intervals (Figure 3).

The excess risk of MZ and ssDZ pairs of the casewise concordance relative to the population-based individual cumulative incidence of depression diagnosis is illustrated in Figure 4, which indicates a familial effect at all ages. The RRR was higher at younger ages, at age 35 the risk was 27.7-fold (95% CI, 20.0-35.5) and 6.9-fold (95% CI, 3.9-9.8) for MZ and ssDZ twins, respectively. At age 90, the corresponding numbers were 3.0 (95% CI, 2.3-3.6) and 1.8 (95% CI, 1.3- 2.2). The secondary outcomes, again, showed a similar pattern (Figure 4).

Stratification by sex led to a casewise concordance risk for male DZ twins that was not significantly different from the cumulative incidence (p=0.357), whereas a significant difference (p=0.002) was found for male MZ twins (Supplementary Figure 3, left). For females, the differences were significant for both DZ and MZ twins (p=0.002 and p<0.001, respectively). For both males and females, the casewise concordance for MZ differed significantly from the casewise concordance for DZ twins (P=0.007 respectively p=0.03). The heritability estimates were around 15% for both males and females (Supplementary Figure 3). In male twins with a co-twin with depression, the RRR at age 90 was 5.2-fold (95% CI, 3.2 7.2) and 2.0-fold (95% CI, 0.9 3.2) higher in MZ twins than in DZ twins. The corresponding numbers in females at age 90 were 2.8 (95% CI, 2.0- 3.5) and 1.8 (95% CI,1.3-2.3), respectively (Supplementary Figure 4).

DISCUSSION

In this cohort study, we included 23,498 MZ and 39,540 DZ twins to examine familial risk and heritability of depression by age at onset in models that take censoring and competing risk of death into account. An indicated familial risk of depression, caused either by genes or shared environment, seemed to decrease slightly with age at diagnosis and a higher concordance risk for MZ over DZ pairs suggested a genetic contribution to the development of depression. The highest estimates of heritability were also seen in younger ages.

Our result showing a significant familial risk of being diagnosed with depression was similar to the findings of previous twin studies(24), although previous studies estimated heritability using structural equation modelling and thus did not account for censoring and competing risk of death. The higher heritability estimates at younger age at first depression diagnosis were supported

by results from a study using the Vietnam Era Twin Register that included 1,874 MZ and 1,498 ssDZ male twins(9). The authors reported that the heritability of depression was 47% for depression onset below age 30 and 10 % for depression onset after age 30. Similarly, in a Swedish family study, the risk of depression given depression in a sibling was highest for onset before the age of 30 with a slight gradual decrease in risk for onset after the age of 30(25). In contrast, a large study of 7,863 MZ and 15,815 DZ Dutch twins aged 12-63 found that heritability estimates of self-reported (or in childhood, maternally-reported) depressive symptoms did not vary with age(26). The authors found that the heritability was between 50-70% in childhood, but 35-50% in adulthood. This difference was mainly due to an increase in environmental variance with age, which leads to a relatively lower influence of genetic factors and might also explain the decrease in heritability with age at first diagnosis in our study. It intuitively makes sense that later-onset depression might be the vascular type (27,28) and more influenced by environmental factors potentially not shared between siblings, such as chronic diseases, vascular dysfunction, metabolic or more prominent lifestyle risk factors. The heritability of depression has in most previous twin studies been reported to be somewhat higher than in our study, with estimates of around 37% (95% CI, 31-42%) in community samples and a slightly higher heritability in clinical samples(5), whereas some family studies have reported lower estimates(11). Our estimates of heritability were between 15-34%, depending on age, which may also be due to our methods of estimating heritability, whereas most previous studies, as noted above, estimate heritability in models derived from a structural equation model that does not account for censoring. Differences in heritability estimates across studies could also be explained by differences in the distribution of other contributing risk factors, such as lifestyle, chronic diseases, and social stressors in the twin populations.

Familial risk and heritability did not seem to vary by sex, but the estimates were imprecise, especially for male twins. Thus, our results could not support or rebut the findings from the Swedish twin register where female depression showed higher heritability than male(6).

A strength of our study is the large cohort of MZ and ss DZ twins, as well as almost complete follow-up through national registers. Supplementary analyses also showed that the lifetime risk of depression observed in our twin cohort was very similar to that of the background population and previous studies(23), indicating that our twin study is representative. However, using register data, we were limited to hospital discharge diagnoses that may not include the milder episodes of depression treated in primary care or the exact age of symptom onset. To explore whether such potential misclassification could have influenced our results, we added purchase of

antidepressant medication as a secondary outcome, and this supported our findings. A limitation of this approach is to assume that antidepressant medication is prescribed for depression, which may only be true for 80% of cases(29). Thus, some antidepressants may also be prescribed for other conditions, such as anxiety, sleeping disorders, and neuropathic pain. The validity of depression diagnoses in the National Patient Registry and the Psychiatric Central Research Register is reported to be of high quality(30), but the concept of depression seems to be broader in the ICD-10 than in ICD-8(31). Patients diagnosed at outpatient visits were first included in the register after 1994, but we found no systematic difference in the proportion of outpatient diagnosis across birth cohorts. Furthermore, we did not have information on depression before middle age in the oldest twins included, as the Psychiatric Central Research Register started in 1969 and we do not know whether these represented incident cases. However, since twins are born on the same day, we find it less likely that these changes over calendar time would influence our within-twin pair comparisons. Although the twin sample was large, we did not have sufficient number of depression cases with onset before age 35 or recurrent event to calculate estimates with sufficient precision for these outcomes. Given the long age span at which depression occurs, long-term follow-up provides greater clarity on estimates of familial risk and heritability by allowing the cohort to attain sufficient age. On a related note, some individuals at risk of developing depression may also be at higher risk of dying from another condition, thus influencing the estimates. Our statistical approach addressed this challenge and accounted for censoring and competing cases of death. Thus, the reported findings on genetic and environmental influences from this observational twin register study provide better insight into the reasons why individuals differ in their susceptibility to develop depression.

In conclusion, in this large cohort of Danish twins an indicated familial risk of depression caused either by genes or shared environment seemed to slightly decrease with age at diagnosis, and an elevated concordance risk for MZ over ssDZ pairs suggested a genetic contribution to the development of depression. Familial risk and heritability did not seem to vary by sex, but the estimates were imprecise, especially for male twins.

Conflicts of interest: The authors declare that they have no financial relationships with any organization that might have an interest in the submitted work and they have no other relationships or activities that could appear to have influenced the submitted work.

Author contributions: All authors were involved in study design and participated in discussing the progress of analyses and the interpretation of findings. MV did the analyses and MKWA wrote the first draft of the manuscript. All authors were involved in the drafting of the manuscript and revision for intellectual content, approved the final version prior to publication, and agree to be held accountable for the work. MO and MV is the guarantor for the data and the analyses.

Ethical approval: The study was approved by the regional data protection agency. No individual-level consent was required, and all data used were anonymized.

REFERENCES

1. SHIH RA, BELMONTE PL, ZANDI PP. A review of the evidence from family, twin and adoption studies for a genetic contribution to adult psychiatric disorders. Int Rev Psychiatry 2004;**16**:260–283.
2. BOOMSMA D, BUSJAHN A, PELTONEN L. Classical twin studies and beyond. Nat Rev Genet 2002;**3**:872–882.
3. HALL JG. Twinning. Lancet 2003;**362**:735–743.
4. BERTELSEN A, HARVALD B, HAUGE M. A Danish twin study of manic-depressive disorders. Br J Psychiatry 1977;**130**:330–351.
5. SULLIVAN PF, NEALE MC, KENDLER KS. Genetic epidemiology of major depression: review and meta-analysis. The American journal of psychiatry 2000;**157**:1552–1562.
6. KENDLER KS, PRESCOTT CA. A population-based twin study of lifetime major depression in men and women. Arch Gen Psychiatry 1999;**56**:39–44.
7. KENDLER KS, GATZ M, GARDNER CO, PEDERSEN NL. A Swedish national twin study of lifetime major depression. Am J Psychiatry 2006;**163**:109–114.
8. POWER RA, KEERS R, NG MY et al. Dissecting the genetic heterogeneity of depression through age at onset. Am J Med Genet B Neuropsychiatr Genet 2012;**159B**:859–868.

9. LYONS MJ, EISEN SA, GOLDBERG J et al. A registry-based twin study of depression in men. Arch Gen Psychiatry 1998;**55**:468–472.

10. JOHNSON W, MCGUE M, GAIST D, VAUPEL JW, CHRISTENSEN K. Frequency and heritability of depression symptomatology in the second half of life: evidence from Danish twins over 45. Psychol Med 2002;**32**:1175–1185.

11. FERNANDEZ-PUJALS AM, ADAMS MJ, THOMSON P et al. Epidemiology and Heritability of Major Depressive Disorder, Stratified by Age of Onset, Sex, and Illness Course in Generation Scotland: Scottish Family Health Study (GS:SFHS). PLoS ONE 2015;**10**:e0142197.

12. GBD 2013 MORTALITY AND CAUSES OF DEATH COLLABORATORS. Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet 2015;**385**:117–171.

13. SKYTTHE A, CHRISTIANSEN L, KYVIK KO et al. The Danish Twin Registry: linking surveys, national registers, and biological information. Twin Res Hum Genet 2013;**16**:104–111.

14. PEDERSEN CB, GOTZSCHE H, MOLLER JO, MORTENSEN PB. The Danish Civil Registration System. A cohort of eight million persons. Dan Med Bull 2006;**53**:441–449.

15. SKYTTHE A, KYVIK K, HOLM NV, VAUPEL JW, CHRISTENSEN K. The Danish Twin Registry: 127 birth cohorts of twins. Twin Res 2002;**5**:352–357.

16. CHRISTIANSEN L, FREDERIKSEN H, SCHOUSBOE K et al. Age- and sex-differences in the validity of questionnaire-based zygosity in twins. Twin Res 2003;**6**:275–278.

17. MORS O, PERTO GP, MORTENSEN PB. The Danish Psychiatric Central Research Register. Scandinavian Journal of Public Health 2011;**39**:54–57.

18. SCHMIDT M, SCHMIDT SA, SANDEGAARD JL, EHRENSTEIN V, PEDERSEN L, SORENSEN HT. The Danish National Patient Registry: a review of content, data quality, and research potential. Clinical epidemiology 2015;**7**:449–490.

19. POTTEGARD A, SCHMIDT SA, WALLACH-KILDEMOES H, SORENSEN HT, HALLAS J, SCHMIDT M. Data Resource Profile: The Danish National Prescription Registry. International journal of epidemiology Published Online First: 27 October 2016. doi:10.1093/ije/dyw213

20. SCHEIKE TH, ZHANG M-J. Analyzing Competing Risk Data Using the R timereg Package. J Stat Softw 2011;**38**.

21. SCHEIKE TH, HOLST KK, HJELMBORG JB. Estimating heritability for cause specific mortality based on twin studies. Lifetime Data Anal 2014;**20**:210–233.

22. holst kk: mets analysis of multivariate event times 2018 - Google-søgning. https://www.google.dk/search?sxsrf=ALeKk03zbgnoMu2k_LQPe3kZAPWvODWBVg%3A1586447967361&source=hp&ei=X0aPXveHE5GMrwTrwojQCg&q=holst+kk%3A+mets+analysis+of+multivariate+event+times+2018&oq=ho&gs_lcp=CgZwc3ktYWIQARgAMgQIIxAnMgQIIxAnMgQIABBDMgQIABBDMgQIABBDMgUIABCDATIECAAQQzIECAAQQzIECAAQQzICCAA6BwgjEOoCECdKEggXEg4wZzk2Zzk1ZzgyZzExM0oNCBgSCTBnMmcyZzFnMVDgA1jHJWDINWgFcAB4AIABbIgBjQSSAQM1LjGYAQCgAQGqAQdnd3Mtd2I6sAEK&sclient=psy-ab (accessed 9 Apr2020).

23. PEDERSEN CB, MORS O, BERTELSEN A et al. A comprehensive nationwide study of the incidence rate and lifetime risk for treated mental disorders. JAMA psychiatry 2014;**71**:573–581.

24. KENDLER KS, OHLSSON H, LICHTENSTEIN P, SUNDQUIST J, SUNDQUIST K. The Genetic Epidemiology of Treated Major Depression in Sweden. American Journal of Psychiatry 2018;**175**:1137–1144.

25. LI X, SUNDQUIST K, HEMMINKI K, SUNDQUIST J. Familial risks for depression among siblings based on hospitalizations in Sweden. Psychiatr Genet 2008;**18**:80–84.

26. NIVARD MG, DOLAN CV, KENDLER KS et al. Stability in symptoms of anxiety and depression as a function of genotype and environment: a longitudinal twin study from ages 3 to 63 years. Psychol Med 2015;**45**:1039–1049.

27. TAYLOR WD, AIZENSTEIN HJ, ALEXOPOULOS GS. The vascular depression hypothesis: mechanisms linking vascular disease with depression. Mol Psychiatry 2013;**18**:963–974.

28. VAN AGTMAAL MJM, HOUBEN AJHM, POUWER F, STEHOUWER CDA, SCHRAM MT. Association of Microvascular Dysfunction With Late-Life Depression: A Systematic Review and Meta-analysis. JAMA Psychiatry 2017;**74**:729–739.

29. HENRIKSSON S, BOËTHIUS G, HÅKANSSON J, ISACSSON G. Indications for and outcome of antidepressant medication in a general population: a prescription database and medical record study, in Jämtland county, Sweden, 1995. Acta Psychiatr Scand 2003;**108**:427–431.

30. KESSING L. Validity of diagnoses and other clinical register data in patients with affective disorder. Eur Psychiatry 1998;**13**:392–398.

31. KESSING L. A comparison of ICD-8 and ICD-10 diagnoses of affective disorder -a case register study from Denmark. Eur Psychiatry 1998;**13**:342–345.

TABLES

Table 1. Basic characteristics of the twin cohort

	Monozygotic	Dizygotic	Total
No. (%)	23,498 (37.3)	39,540 (62.7)	63,038
Age at diagnosis (mean [SD])	43.2 (19.1)	47.7 (19.0)	46.1 (19.1)
Female, N (%)	11,906 (50.7)	19,088 (48.3)	30,994 (49.2)
No. of depression outcomes	538 (2.3)	1007 (2.5)	1545 (2.4)
No. with antidepressant use	4358 (18.5)	7206 (18.2)	11 567 (18.3)
No. of pairs			
Concordant for non-depression, N	11,256	13,800	30,056
Discordant for depression, N	448	933	1,381
Concordant for depression, N	45	37	82

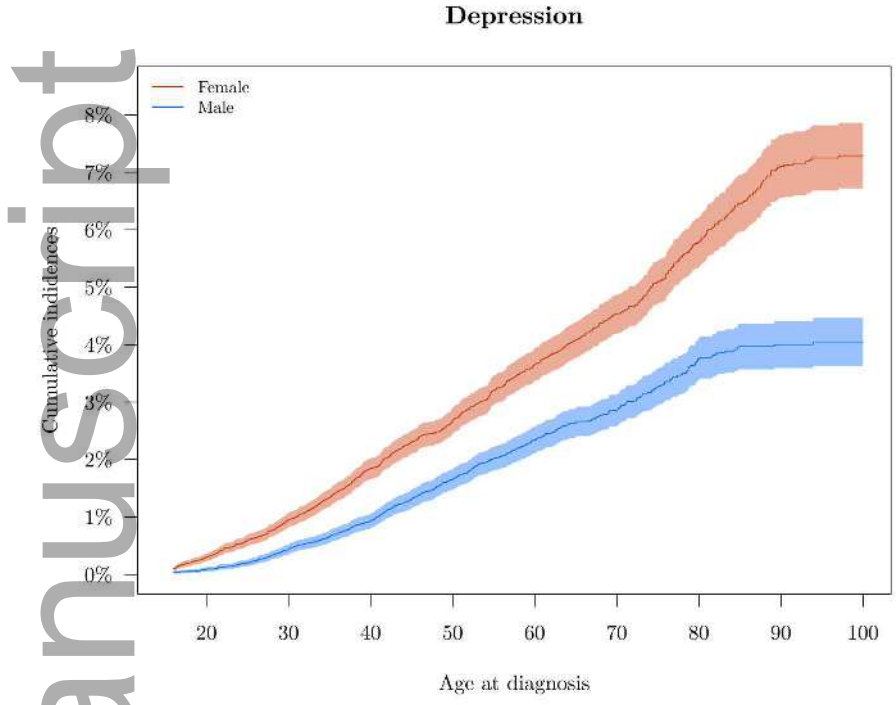
FIGURE LEGENDS

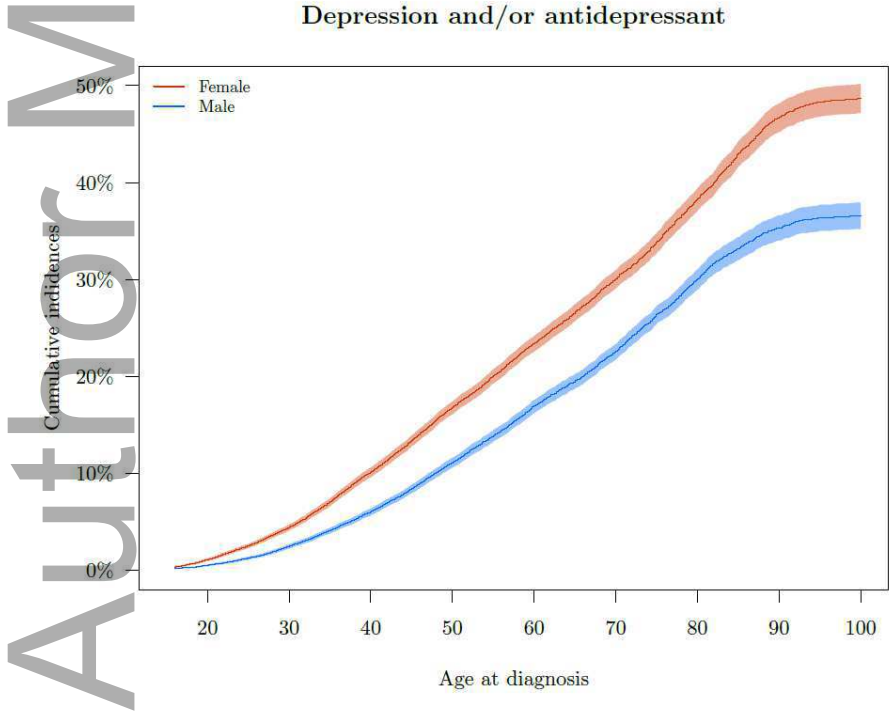
Figure 1. The cumulative incidence of depression (top) and depression and/or antidepressant use (bottom) in 23,498 monozygotic twins and 39,540 same-sex dizygotic twins from the Danish Twin Registry.

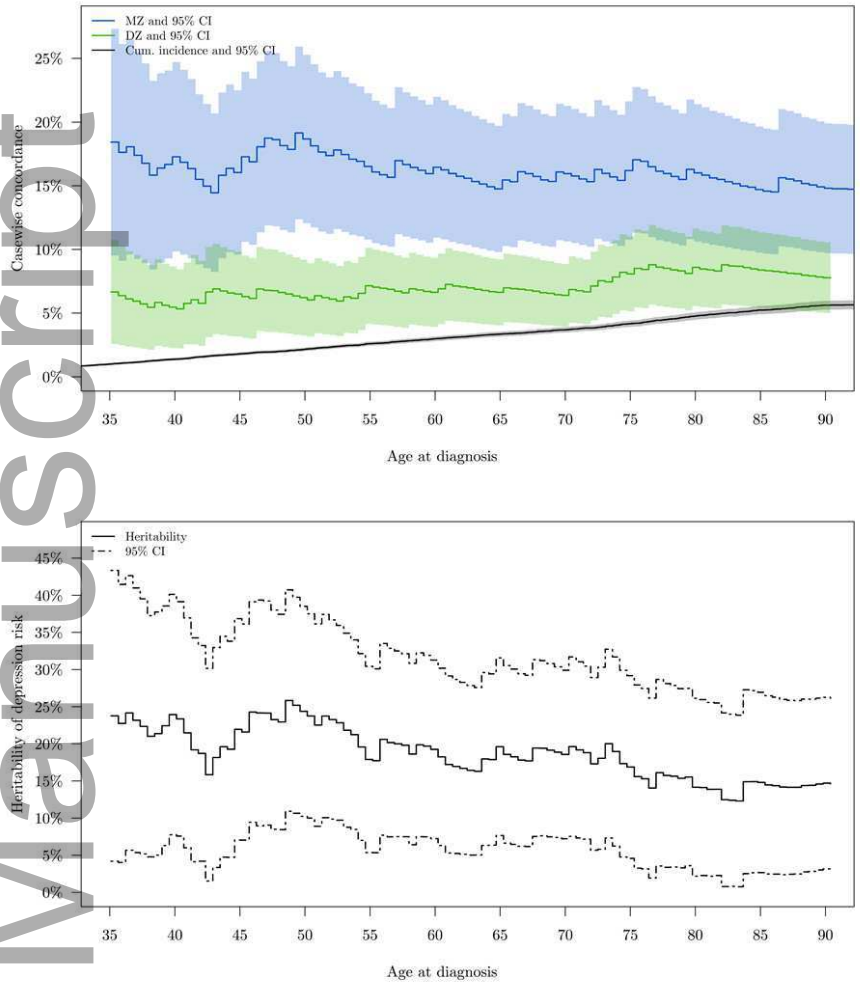
Figure 2. Casewise concordance of depression among monozygotic (MZ) and same-sex dizygotic twins (DZ) are shown in the top figure. The squared cumulative incidence of depression in the entire twin population is shown in gray and represents the expected concordance between twins if no genetic or familial effects were present. Below is a plot of the heritability (difference between MZ and DZ twins) across age with exact estimates with 95% confidence intervals at specific ages. CI=confidence interval. Cum. incidence=cumulative incidence.

Figure 3. Casewise concordance of depression and/or antidepressant use among monozygotic (MZ) and same-sex dizygotic twins (DZ) are shown in the top figure. The squared cumulative incidence of depression and/or antidepressant use in the entire twin population is shown in gray. Below is a plot of the heritability (difference between MZ and DZ twins) across age with exact estimates with 95% confidence intervals at specific ages. CI=confidence interval. Cum. incidence=cumulative incidence.

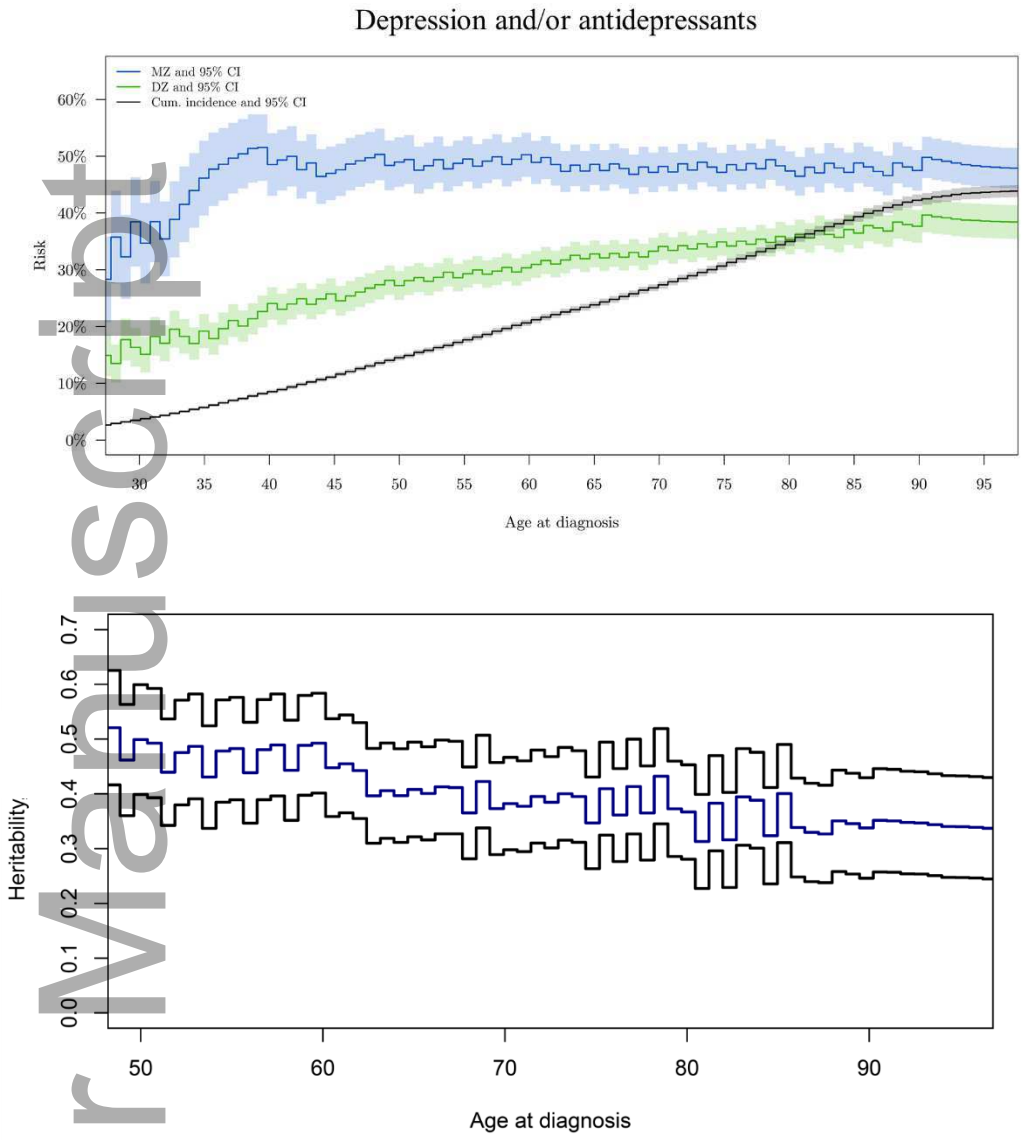
Figure 4. Relative recurrence risk ratio (RRR) of depression (top) and depression and/or antidepressant use (bottom) in monozygotic (MZ) and dizygotic (DZ) pairs compared to population risk, by age at first diagnosis. CI=confidence interval



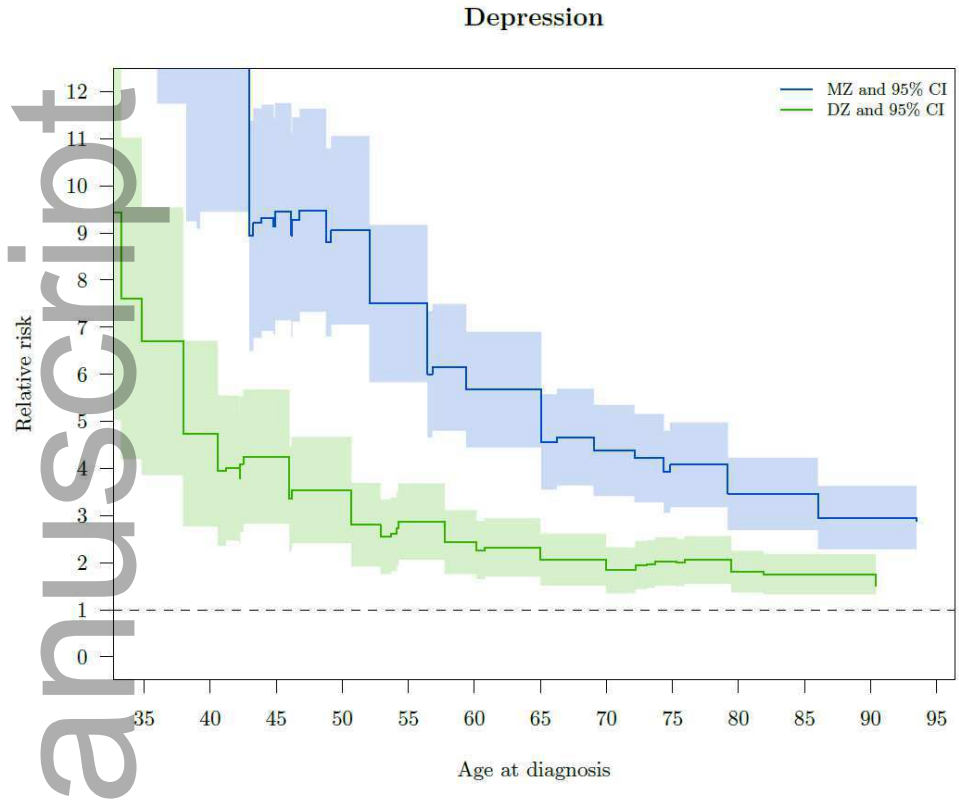


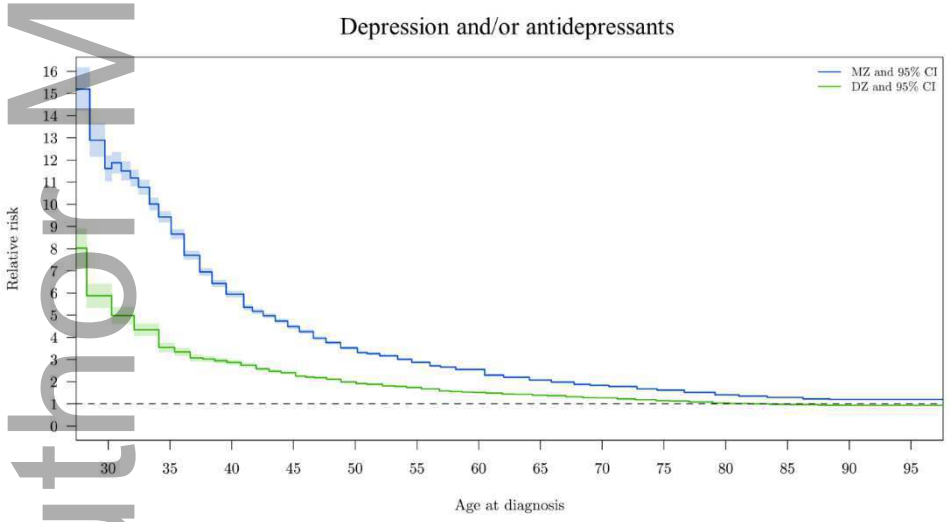


Estimate\age	35	50	60	70	**80**	90
	Casewise concordance risk (CCR) and cumulative incidence fraction (CIF) in % (95% CI)					
CCR (MZ)	18.5(9-27.1)	18.7 (12.1-25.3)	16.5(10.9-22)	16(10.6-21.3)	16(10.6-21.4)	14.8(9.7-19.9)
(DZ)	6.6(11-2)	6.2(3.2-9.2)	6.6(3.9-9.3)	6.4(3.9-8.9)	8.6(5.6-11.6)	14.8(9.7-20)
CIF	1(0.9-1.1)	2.1(2-2.3)	3(2.8-3.2)	3.7(3.5-3.9)	4.8(4.5-5.1)	5.6(5.3-6)
			Heritability in % (95% CI)			
	24.8(4.6-43.1)	24.4(10.2-38.5)	19.3(7.2-31.3)	18.6(7.2-29.9)	14.2(2.2-26.1)	14.7(3.2-26.3)



Estimate\age	35	50	60	70	80	90
	Casewise concordance risk (CCR) and cumulative incidence fraction (CIF) (95% CI)					
CCR (MZ)	29(21-36)	46.2(42.4-49.9)	46.3(43.1-49.6)	46.7(43.6-49.8)	46.2(43.1-49.8)	48.1(44.9-51.2)
(DZ)	15(19-11)	26.1(24-28.2)	30.4(28.5-32.3)	32.1(30.2-34)	34(32-35.9)	36.7(34.5-38.9)
CIF	7(6-8)	13.9(13.4-14.3)	20.1(19.5-20.6)	26.2(25.6-26.8)	34.1(33.3-34.9)	41.3(40.2-42.3)
			Heritability in % (95% CI)			
		50 (40-60)	50(40-60)	42(30-50)	40(30-50)	38(29-44)





Estimate\age	35	50	60	70	**80**	90
			Depression (95% CI)			
RRR (MZ)	27.7(20-35.5)	9.2(7.2-11.3)	5.7(4.5-7)	4.4(3.4-5.4)	3.5(2.7-4.3)	3(2.3-3.6)
(DZ)	6.9(3.9-9.8)	3.6(2.4-4.9)	2.5(1.8-3.2)	1.9(1.5-2.7)	1.8(1.4-2.3)	1.8(1.3-2.2)
			Depression and/or antidepressants (95% CI)			
RRR (MZ)	8(7.9-8)	3.6(3.5-3.7)	2.5(2.5-2.6)	1.9(1.8-1.9)	1.4(1.4-1.5)	1.2(1.2-1.2)
(DZ)	3.4(3.3-3.5)	2.0(2.0-2.1)	1.5(1.5-1.6)	1.3(1.3-1.3)	1.1(1.0-1.0)	0.9(0.9-1.0)